2008 Franklin Institute Awards

Benjamin Franklin Medal in Life Science

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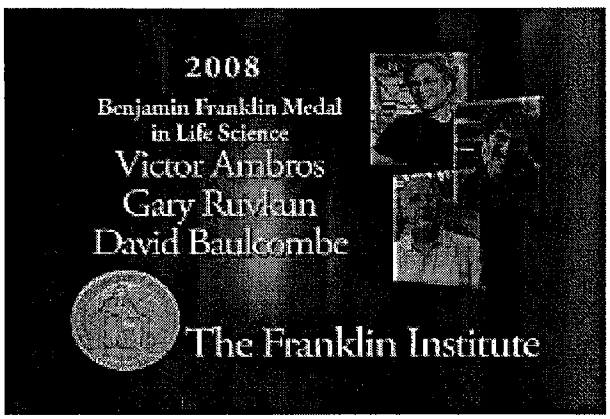


Victor R. Ambros, Ph.D.

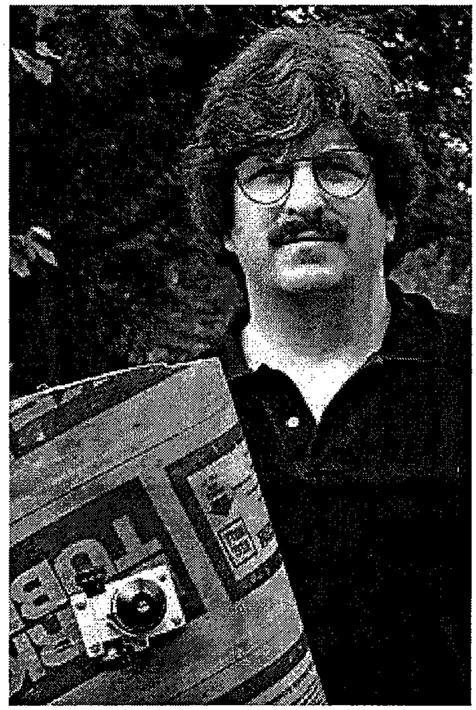
Professor, Program in Molecular Medicine
University of Massachusetts Medical School
Worcester, Massachusetts

Gary Ruvkun, Ph.D.

Professor of Genetics

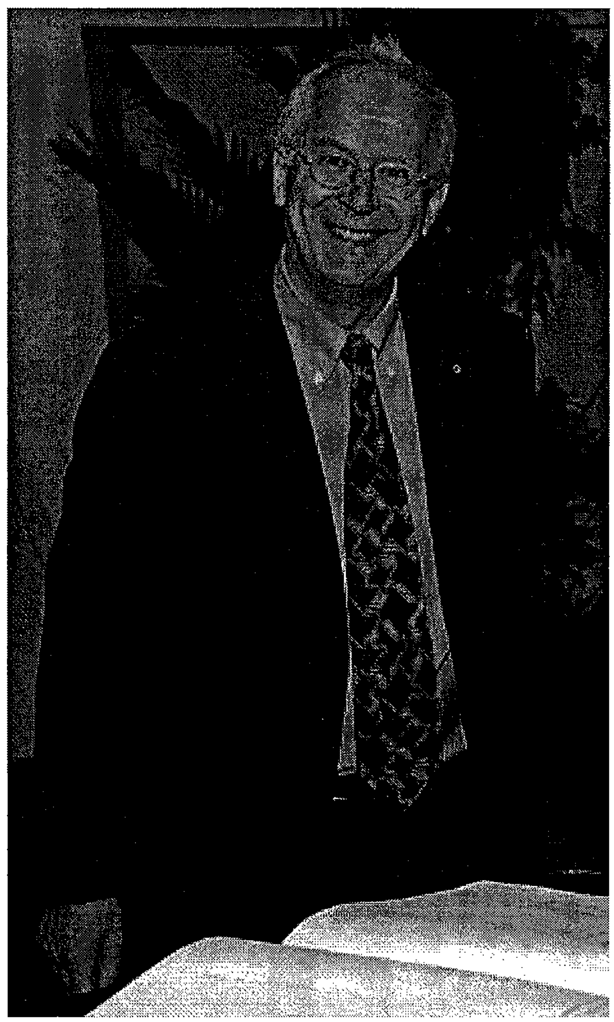
EXHIBIT B

Harvard Medical School
Department of Molecular Biology
Massachusetts General Hospital
Boston, Massachusetts



David Baulcombe, Ph.D., FRS

Professor of Botany
Royal Society Research Professor
Department of Plant Sciences
University of Cambridge
Cambridge, United Kingdom



Year: 2008

Subject: Life Science

Award: Benjamin Franklin Medal in Life Science

Citation: The 2008 Benjamin Franklin Medal in Life Science is presented to Victor Ambros, Gary Ruvkun and David Baulcombe for their discovery of small RNAs that turn off genes. Their pioneering work initiated a paradigm shift in our perception of the ways genes are regulated, and this insight is making possible major new genetic tools for basic research, and for improving agriculture and human health.

Understanding how DNA and RNA work inside plants and animals has far-reaching implications for combating disease, raising virus-resistant crops and extending the longevity of cells -- and people. The genes inside cells churn out proteins to govern all their systems -- from how to build cellular structures to whether a cell lives or dies -- and for decades RNA was thought merely to assist production of those proteins. The paradigm of that understanding was well-entrenched in the 1990s, before the work of Victor Ambros, Gary Ruvkun and David Baulcombe helped turn it upside-down, showing that the role of RNA had a much wider scope. Through their research, done jointly and in parallel, these scientists discovered tiny strands of RNA some 20 nucleotides long, which could turn genes off and prevent them from functioning -- gene "silencing." Their work has set off an onslaught of research to study the breadth of important cellular processes influenced by small RNA.

Biographical Information

Victor Ambros

Victor Ambros was born in Hanover, NH in 1953. He attended the Massachusetts Institute of Technology [MIT] for both his S.B. and his Ph.D. in biology -- completing the latter in 1979 with studies of the polio virus genome under his research advisor, Nobel laureate David Baltimore. As a post-doc at MIT, in the early 1980s he began to study the roundworm *Caenorhabditis elegans* hoping that a creature so useful for the study of genetic mutations could teach him about cell division and cell death. He joined the faculty at Harvard in 1985, then moved his lab in 1992 to Dartmouth College, where he remained for about 15 years.

In 1993 Ambros spotted a 22-nucleotide RNA now called *lin-4* miRNA. He and Gary Ruvkun showed that it had a functional role in the developmental timing of cells: *lin-4* RNA interacted with the first product of a target gene, thus inhibiting its function. At first it was not clear whether such functional RNA might be seen anywhere outside of the worms he was studying, and the research was initially underappreciated. By 1999, however, David Baulcombe's work spotting small (or micro-) RNAs associated with gene silencing in plants helped catapult the work to the forefront. This was also fueled by a report the next year from Ruvkun who found a second miRNA that was present not only in *C. elegans*, but also in other animals including humans. Soon, many more miRNAs were discovered, and scientists began to research them in earnest, discovering that these snippets help control numerous biological functions including cell development and death, muscle development and oncogenesis.

This year Ambros joined the University of Massachusetts Medical School where he continues to study *C. elegans*, as well as the fruit fly, to further understand how microRNAs play a role in the temporal control of these animals' development. Ambros is a member of the National Academy of Sciences and his awards include AAAS's Newcomb Cleveland Prize, Brandeis's Lewis S. Rosenstiel Award and the Genetics Society of America Medal for outstanding contributions in the past 15 years.

Gary Ruvkun

Gary Ruvkun earned an A.B. in biophysics from the University of California at Berkeley in 1973 and his Ph.D. from Harvard in biophysics in 1982. His post-doctoral research at Harvard was done with two Nobel Prize winners: Walter Gilbert at Harvard and Robert Horvitz, who was at MIT. Ruvkun began to work with the roundworm *C. elegans* studying genes that control timing of development. In 1985 he joined the faculty of Harvard Medical School, where he remains today as a professor of genetics.

The Ruvkun lab worked in concert with Victor Ambros, who had also done post-doctoral work with Horvitz. In 1993 the groups discovered a short strand of RNA in *C. elegans* that, instead of helping to churn out proteins -- the sole job RNA was thought to do -- performed specialized functional work on the cell. The strand, known as *lin-4*, helped in the genetic pathway of developmental timing for the cell by interacting with the first product of a target gene to block its function. Several years later, Ruvkun discovered a second small RNA of this type, called *let-7* and found it existed in a wide range of other animals, thus suggesting these microRNAs, as they are now called, were indeed ubiquitous.

Ruvkun has gone on to computationally find hundreds of these short RNAs; he refers to them as 'the dark matter of genetics,' since there are so many and they are so important, yet until a few years ago they went undetected. He also studies aging, fat and molting, among other topics, and the roles of microRNAs in some of these.

He has not abandoned his original roundworm, as he attempts to discover the components of the microRNA pathways in *C. elegans*. Ruvkun has written over 100 research papers and has several issued and pending patents. He is the recipient of an NIH Merit Award and the Rosenstiel Award from Brandeis University.

David Baulcombe

Born in 1952 David Baulcombe attended Leeds University where he earned a B.S. in botany in 1973. He went on to receive a Ph.D. from the University of Edinburgh in 1977. Baulcombe was a post-doc at McGill University and at the University of Georgia before establishing a research group at the Plant Breeding Institute in Cambridge. In 1988 he joined the Sainsbury Laboratory, where he did much of his world-renowned work. He is moving his laboratory to the University of Cambridge, where he is now a professor of botany.

Baulcombe's interest in plant genetics came from his interest in virus resistance. In the 1990s his group began studying gene silencing since they suspected -- and later showed -- it was one way a plant could naturally defend itself against viruses. The researchers published a seminal paper in 1999 stating that small RNA strands were associated with several examples of gene silencing, including one related to viral defense. They deduced that the newly discovered small RNAs, now known as small interfering RNAs or siRNAs, guided the silencing to the right targets. Gary Ruvkun and Victor Ambros had previously published on the existence of a similar small RNA strand (an RNA type now called miRNA), but this had not yet gained much attention. Baulcombe's details of this silencing mechanism helped bring the earlier research into the limelight as did Ruvkun's discovery of a second miRNA, published in 2000. Suddenly there was a new, more complex image of how RNA worked. Small RNA's heretofore unknown job inside cells fueled new work to hammer out the details.

Not only did this discovery catalyze research into a whole family of genetic mechanisms, but it also opened the door for unprecedented control over genes. It helped prove a conceptual framework for

interpreting, with the Nobel Prize winning work of Fire and Mello who showed that long double-stranded RNA could silence genes, a process called RNA interference or RNAi. A unifying principle soon showed that the long double-stranded RNA was being chopped into small RNAs to guide the silencing. For basic research, using siRNA to shut off a gene is a great way to figure out just what that gene does. The Baulcombe lab has made very important contributions to this by co-opting viruses to shut off specific genes in plant hosts. On a medical level, small RNAs might be the basis of new drugs to silence disease or virus genes. It is this latter area that Baulcombe continues to research, hoping to protect plants from attack. He also studies how silencing directed by RNA affects growth and development.

Baulcombe is a Fellow of the Royal Society and a foreign associate member of the U.S. National Academy of Sciences. His awards include the Royal Medal, the Massry Prize, the MW Beijerinck Virology Prize, the Wiley Prize in Biomedical Science, the Ruth Allen Award and the Kumho Science International Award in Plant Molecular Biology and Biotechnology.